

Multivariate statistical approach in food and pharmaceutical quality control

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Abstract

IR spectra contain chemical information of matter and can be acquired from raw/untreated samples. The spectra are, however, complicated to interpret and could not be used directly for both qualitative and quantitative purposes. In this research a statistical approach namely, multivariate data analysis (MVDA) or chemometrics was employed for mining information related to chemical compositions from spectroscopic data. Two examples are used to illustrate the potential of this approach, one is edible oil (using benchtop FT-IR), and pharmaceuticals (using handheld NIR). Olive oil was differentiated from adulterants (sesame, sunflower, palm oil) in PCA, and the content of olive oil was successfully determined by the PLS model the error of olive oil content < 5%. Norfloxacin content in lab-scale powder formulation yield the auspicious results with the error < 6%. The results proved the developed techniques are promising for rapid analysis at significantly lower costs.

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Keyword

food and pharmaceutical quality, chemometrics, handheld NIR, FTIR, multivariate data analysis

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1 Introduction

Quality assurance and quality control in food and pharmaceutical industries are crucial for the protection of consumer health. Conventional analytical methods (*e.g.* gas/liquid chromatography) are well established but costly and time consuming. Lengthy sample treatment procedures, state-of-art instruments and skilled personnel are main obstacles preventing high frequencies of testing especially in developing countries. Efforts have been made to develop fast and low-cost techniques to meet the increasing demands[1-3].

Data collected from analytical instruments *e.g.* IR, UV, Raman, NMR or mass spectrophotometers contains a huge sum of information related to chemical compositions of samples. Though often visualized into 2-D spectra for observation, in most cases, the data is too complicated to apply normal calibration method to get reliable results. The task is even unfeasible for multi-quantitation of several components in mixtures. Nowadays with the aid of multivariate data analysis (MVDA), useful information can be easily drawn from such huge data sets of up to hundreds

of variables. This approach is invaluable in process analytical chemistry for outlier detection, classification and quantification purposes. It could also open to the high throughput and the ability of automation.

In MVDA, principle component analysis (PCA) is the most basic one which converts variables of the original data into a new set of reduced number of variables called “principal components” (PC) or “latent variables”. Other than simplifying data, helping us to visualize the datasets PCA can also identify new meaningful underlying variables. For classification and quantification purposes, projections to latent structures by means of partial least squares (PLS) method is employed. PLS-DA technique (DA stands for discrimination analysis) processes matrix X (N rows for N samples & K columns for K observed characteristics) and “dummy” matrix Y containing N rows for N samples and M columns represents M groups. PLS is also a main technique for quantification of interested components in samples. In this case Y matrix containing the chemical compositions[4]. In this work MVDA approach was applied to IR spectra to study (i) the adulteration of olive oil and (ii) pharmaceutical

classification and quantitation. (i) Olive oil has various health benefits *e.g.* prolonging life expectancy, anti-inflammatory, preventing cardiovascular diseases and reducing risks of tumors development. The trade value of olive oil, especially the refined pure extract from olive which often branded “extra virgin” is, therefore, very high. Many manufacturers add low-price oils *e.g.* soybean, sunflower or palm olein oil into olive oil for more benefits[5]. In this study, efforts were made to differentiate olive oil and the other edible oils and to estimate of adulterant levels in olive oil. Several international publications have predicted olive oil adulterants with high accuracy using chemometric[6,7], but few in Vietnam exist. (ii) The Vietnam Ministry of Health has issued Circular 11/2018, required sampling and identification of every in-coming raw material before being manufactured, which becomes a heavy burden for local pharmaceutical companies with respect to the cost and time. The qualification process is often done with Raman or NIR spectroscopy by comparing the raw material spectra with a pre-built spectra library[3]. Since instruments with data processing software and database are very expensive, cost-effective screening methods are in strong demand. In recent years, progresses have been made applying multivariate approach to NIR spectrophotometry (NIRS) in the field of pharmacy. On classification and screening raw materials, not only traditional models PCA or PLS-DA have been used, but also advanced ones such as Support Vector Machine (SVM)[8] and Artificial Neural Network (ANN)[9]. Detecting counterfeit tablets were also shown feasible results using miniature device[10,11]. Regarding qualitative analysis, a number of publications have focused in determination of chemical compound content such as active pharmaceutical ingredients (API), excipients or moisture in pharmaceuticals. They could be in various forms *e.g.* powders, granulates, tablets with or without coatings, gels, films or lyophilized vials[12]. Many APIs have been studied using bench-top NIR or FT-IR, including indapamide[13], paracetamol[14], etc. Studies using handheld NIRS, however, were less reported. Alcalá *et al.* performed quantitative determination of the three crystalline active ingredients namely, acetylsalicylic acid, ascorbic acid and caffeine in blends with the two amorphous excipients cellulose and starch, competitive predictions comparable to results from benchtop counterparts[15,16]. Such studies in Viet Nam are fairly rare, though, notable ones were conducted in Hanoi University of Science determining the content of several antibiotics using benchtop FT-IR[17,18]. In this work our efforts are to develop fast, affordable methods requiring minimal sample treatment and low-cost equipment. The objectives are not only on-site screening low quality, fake products but also to perform quantification.

2 Experimental

2.1 Instruments and spectra acquisitions

Two different instruments, a benchtop FTIR in ATR sampling mode (Agilent, Cary 630) and handheld NIR (NIRscan Nano EVM, Texas Instrument) in reflectance mode, were used to acquire characteristic data from edible oils in liquid form and pharmaceuticals in powdered form, respectively. Bench-top Agilent Cary 630 FTIR Spectrometer used 32-scans mode and the scan resolution of 4cm^{-1} , in the wavelength range of $600\text{--}3500\text{cm}^{-1}$. Handheld NIR scan Nano EVM used the 10-scans mode with the scan resolution of 10 nm, in the wavelength range of $900\text{--}1700\text{nm}$. Data obtained was treated by normalize or standard normal variate (SNV), using Spectragryph 1.2.10 (Menges, Germany). Models from pretreated-data were built using SIMCA-P (Umetrics, Sweden) and evaluated by R2X for goodness of fit; R2Y for linearity correlation between factors (X) and responses (Y); Q2X for goodness of prediction, Root Mean Square Error of Estimation – RMSEE and Root Mean Square Error of Prediction- RMSEP[4]. RMSEE and RMSEP are calculated by formulas 1, where $\hat{y}_i$ and y_i are the actual and the estimated/predicted values of y by the model, respectively:

$$RMSE = \sqrt{\frac{\sum_{i=1}^n (\hat{y}_i - y_i)^2}{n}} \quad (1)$$

As for quantitative model, factors (X) are the processed NIR spectra and responses (Y) are the measured parameters (content of olive, content of active ingredients in powder formulation, etc.).

All the weighing was carried out with Mettler Toledo AG245 ($d=0.01\text{mg}/0.1\text{mg}$). Moisture content was determined by thermogravimetric balance (A&D Moisture Analyzer MX-50).

2.2 Experimental for olive oil

Most of oil samples were kindly provided by Vocarimex, a Vietnamese vegetable oil company; few bought from different manufacturers, with and without preservatives, and stored in various conditions as to reflect the complexity. Mixtures of oil were prepared by weighing, then thoroughly mixed for 3-5 minutes by vortex. GC-FID was used to determine the fatty acid contents and compared with those set by National Vietnam Standards (TCVN).

2.3 Experimental for pharmaceutical samples

2.3.1 Classification study

NIR spectrum acquisition was conducted in warehouses of a local pharmaceutical company in Ho Chi Minh City with monitored temperature ($20.5 \pm 1^\circ\text{C}$) and humidity ($60 \pm 2\%$). There were 15 common active pharmaceutical ingredients (API) and excipients, namely, amoxicillin, acid ascorbic, avicel, gelatin, povidone, lactose, magnesium lactate

dihydrate, maltodextrin, mephenesin, magnesium stearate, N-acetylcysteine, piroxicam, starch, sucrose, and thiamine. The spectra were acquired either by placing the handheld NIR in contact with polyethylene (PE) container or by encasing the NIR instrument in PE bag and scanned the materials in clean rooms of the company. The latter is used for materials with non-PE or NIR-sensitive packaging. The data set consists of 20-80 spectra corresponding to 20-80 packages containing each material of known origins. Data was separated into two groups, training set for model-building and prediction set to test the model.

2.3.2 Quantification test

Norfloxacin powder was kindly provided by a local company; its standard matches the requirement for drug production. The excipients chosen for the formulation were lactose, povidone, avicel (microcrystalline cellulose), magnesium stearate with the percentage of 65, 30, 4, and 1%, respectively. These values were recommended by the 5th Handbook of Pharmaceutical Excipients and expert pharmacists, as well as it closely resembled commercial products. For calibration set, the concentrations of norfloxacin were varied from 90mg to 500mg. All powder should be dried in oven at 80°C for 15 minutes in order to minimize the interference of moisture. The moisture after sample preparation ranged from 0.6-1%. The mixtures of excipients and API were prepared by weighing and vortex-mixing for 7-10 minutes. Spectra was then collected with the handheld NanoScan in reflectance mode. Direct contact between the NanoScan NIR sapphire glass window and the powders was not preferred, as the particles can contaminate the instrument and vice versa. It is advisable to wear gloves when collecting spectra minimize contact with the window of the instrument. The IR spectra of formulation powder mixtures were obtained by measuring through thin low-density polyethylene (LDPE) packaging (commercial zip bags) in reflection mode. Different materials were tested for this purpose, but LDPE were the most desirable so far, as it was thin enough for not to greatly reduce the signal and allow maximum contact between the samples and the glass window of the handheld NIR.

3 Results and discussion

3.1 Detection of adulteration of olive oil by FTIR

Absorbance at 17 wave numbers from 4 different ranges was then selected as variables. Data points were selected using the wavelengths corresponding to different IR molecular vibrations of various oil samples, as suggested by Rohman, A. et al [19,20] (Table 1). It should be noted that 4 wave numbers in both sides of the selected ones were also involved in the PCA model to avoid possible shifts of this variable during the spectra acquisition

3.1.1 Overview the grouping of edible oils by PCA

The minor differences from wave number shifts and absorbance ratios between peaks are responsible for the oil chemical composition characteristics (Fig. 1). The first two PCs of PCA score plot explained 90 % of the variation in the data set with $R^2 = 0.957$, $Q^2 = 0.947$. From the PCA Score Plot, olive oil locates far from its adulterants. Sunflower oil and soybean oil appear to be overlapped with each other, indicating similar chemical properties, whereas sesame oil and palm olein groups separate well from the others (Fig.2). Comparing with fatty acid profiles determined by GC-FID the locations of olive oil and palm olein oil on the left of PCA Score plot could be explained by the high content ratio of oleic to linoleic acid content ($4 \div 7.5$) while sesame, sunflower and soy bean oils possess low content ratios of these two fatty acids ($0.3 \div 1$)

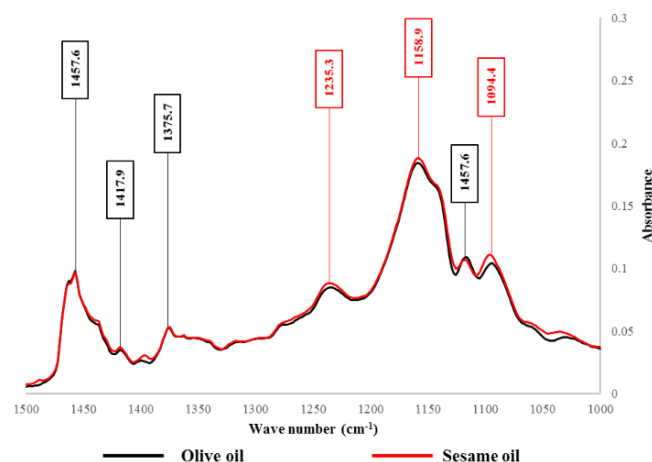


Fig. 1 A zoomed in FTIR spectrum in the range of 1000-1500cm⁻¹ of olive and sesame oil shows little differences (highlighted)

Table 1 List of selected wave number from FTIR spectrums for PCA (reproduced from references^{6,7})

WL range	Selected wave number (cm ⁻¹)	Characteristics
3100-2800 cm ⁻¹ Fluctuating valence region of hydrogen	3004-3008	C-H vibration from = C-H
	2920, 2851	Symmetrical and asymmetric oscillation of the fatty group -CH ₃
1800-1600 cm ⁻¹ Vibrations from pi-bonds	1742	C=O linkage of the carbonyl esters
	1653	C = C of <i>cis</i> olefins
1600-1390 cm ⁻¹ Other stretchings and bendings	1457	Bending from -CH ₂ and -CH ₃ fatty groups
	1395, 1397, 1399	Bending in the plane of <i>cis</i> -olefinic group =CH.
1390-700 cm ⁻¹ Fingerprint regions	1354	CH ₂ bending
	1235, 1160	C – O esters stretching
	1117, 1098	Carbohydrate C-C linkages
	721	CH ₂ librations and bending in outer plane of <i>cis</i> -olefinic groups

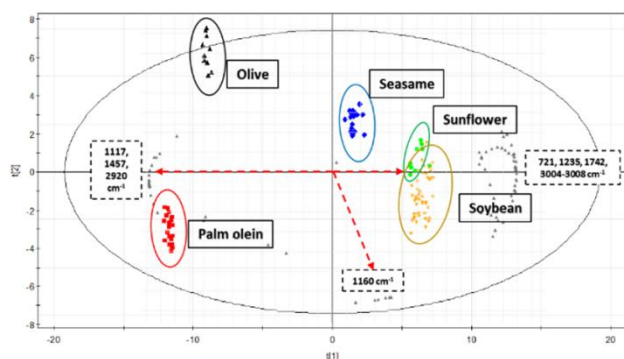


Fig. 2 PCA Scores and Loadings overlay from the FTIR result of five different vegetable oils

3.1.2 Prediction of olive oil content in mixtures with other adulterants by PLS

For the training set, a pure olive oil and 32 mixtures of olive oil with another edible oils namely, sesame, sunflower, soybean, and palm olein oil were prepared with the levels of adulterants ranging from 5-40%. Four mixtures were also prepared as test set.

After several refinement steps (data not shown) a PLS model (5 PC, $R^2X=0.994$, $Q^2X=0.953$) employed first derivative of FTIR spectra and 538 wave numbers (variables) possessing VIP values >1 (VIP) gave the highest accuracy with Root Mean Squared Error of Estimation (RMSEE) and Root Mean Squared Error of Prediction (RMSEP) of 1.1 and 2.9%, respectively and the error of olive oil % < 5% (Table 2). Those results show a promising possibility in predicting mixed oil sample components by PLS regression. In Table 2, the oil contents notated “-” is too low to be predicted with positive values using the models.

Table 2 Comparison between predicted and actual values for percentage of oil in mixtures

Test ID	% Oil in the mixtures					
	Olive		Sesame		Soy bean/ sunflower	
	Actual	Predict	Actual	Predict	Actual	Predicted
A	67.2	67.7 ± 3.9	0	-	32.8	28.3 ± 3.8
B	81.8	80.2 ± 6.7	0	-	18.2	18.8 ± 5.4
C	82.6	85.7 ± 7.6	17.4	10.6 ± 3.3	0	-
D	58.01	60.5 ± 6.7	0	6.3 ± 4.8	42.0	37.3 ± 4.6

For the sunflower and soybean oils, it is recommended to merge these samples as one group since their spectra are very similar.

3.2 Application of handheld NIR in pharmaceutical quality control

3.2.1 Classification of pharmaceutical raw materials

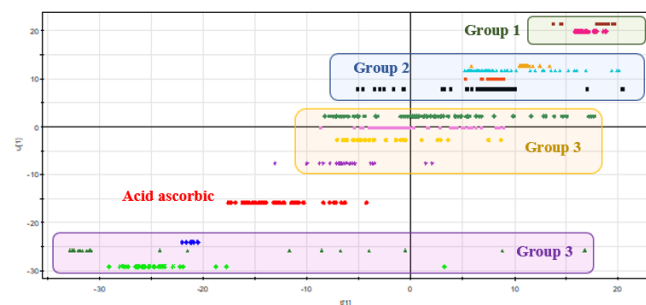


Fig. 3 PLS-DA for 15 compounds

In Figure 3, each data point represented a sample spectra, each class (chemical) is colored accordingly. The PLS-DA model containing all 15 classes/compounds (Fig. 3) shows poor fitness and prediction quality ($R^2X = 0.895$, $Q^2X = 0.866$ with 24 principal components). It is not unexpected since the optimal number of classes in a PLS-DA model should not be larger than 5, therefore, we divided them into 4 groups of 2-4 chemicals which has similar spectra. Among the studied compounds, ascorbic acid has spectra radically different from the others, it is therefore easily differentiated even with PCA model.

Table 3 Classification of 15 pharmaceutical compounds with PLS-DA

	Compound	RMSEE
Group 1 #PC = 5 $R^2X = 0.985$ $R^2Y = 0.95$ $Q^2X = 0.933$	Magnesium stearate	0.0741
	Piroxicam	0.0741
Group 2 #PC = 10 $R^2X = 0.996$ $R^2Y = 0.98$ $Q^2X = 0.964$	Ampicillin	0.0867
	Kollidon30	0.0403
	Mephenesin	0.0814
	Thiamine	0.0608
Group 3 #PC = 10 $R^2X = 0.997$ $R^2Y = 0.968$ $Q^2X = 0.954$	Magnesium lactate	0.1155
	Lactose	0.0990
	Maltodextrin	0.0690
	N-acetylcystein	0.0527
Group 4 #PC = 5 $R^2X = 0.984$ $R^2Y = 0.979$ $Q^2X = 0.939$	Starch	0.0815
	Acid citric	0.0229
	Gelatin	0.0845
N/A	Sucrose	0.0897
	Acid ascorbic	0.0365

Table 3 shows good quality of classification model with low RMSEE values, and high R2X and Q2X. 3 samples were taken for each compound, and therefore, the prediction set has total of $3 \times 15 = 45$ spectra. The PLS-DA model can correctly classify 70% samples at the probability larger than 90%, while the other 30% with lower probability (70-88%). This may be due to the effect of packaging, spectra acquisition method, as well as the quite low resolution of the handheld instrument. Expectedly, the model failed to identify all maltodextrin samples, as it also has an additional matching with sucrose which is the consequence of their similar chemical structures.

3.2.2 Quantification of norfloxacin

In the quantitation study, 24 mixtures of norfloxacin with the excipients were prepared by varying norfloxacin levels from 90-500mg (in 1g formulation). Fig. 4 shows dramatic differences of NFX and EXP spectra in the wavelength range of 1200-1650nm.

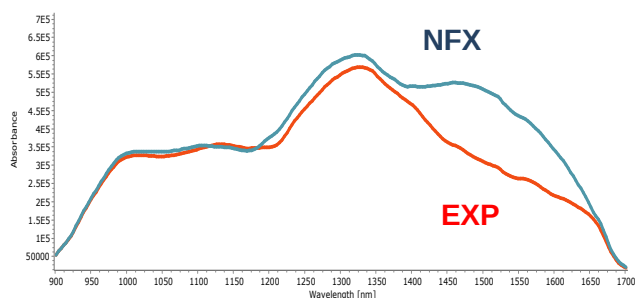


Fig. 4 Spectra of pure norfloxacin (NFX) and excipient mixture (EXP)

During the model refinement, the variables with VIP < 0.7, which lie in the wavelength region of 1660-1690 nm were removed and one outlier outside the Hotelling's T2 eclipse (critical 99%) was dismissed.

The obtained PLS model has 3 PC, R2X=0.990, R2Y=0.986, Q2X=0.966. The actual and predicted levels of norfloxacin were well agreed (Fig.5) with RMSEE and RMSEP of the model was of 0.0280 and 0.02579, respectively. The accuracy is at the same level of published papers. Sarraguca (2009) reported the RMSEP of 0.043 for paracetamol quantification [22], while RMSEP reported by Alcalà *et al.* (2014) is of 0.219 for the mixture acetylsalicylic acid, acid ascorbic and caffeine[16]. Using 4 external testing samples (T1-T4) with concentrations in the calibration range, the errors for our test samples range from 0.77 to 5.25% (Table 4).

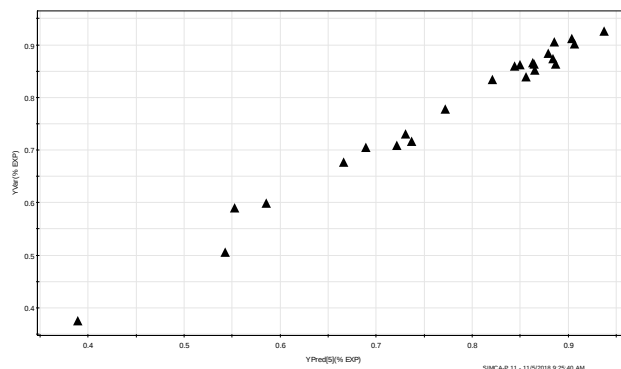


Fig. 5 Actual vs. Predicted Plot of norfloxacin

Table 4 Comparison between predicted and actual values of NFX in test formulations

Sample ID	Actual NFX (mg/g)	Predicted NFX (mg/g)	Error (%)
T1	0.2951	0.3106	5.25
T2	0.2648	0.2592	2.13
T3	0.3619	0.3767	4.12
T4	0.3536	0.3577	1.17

To analyze the robustness of the model, norfloxacin in different matrices (T5-T14) with varying contents of excipients were calculated using the original model. The excipients were varied within suggestion from 5th Handbook of Pharmaceutical Excipients: 20-90% avicel, 40-80% lactose, 0.5-5% povidone, 0.25-5% magnesium stearate. The number of experiments was generated by D-Optimal (Design of Experiment). It was found that the errors are much greater with varying excipients (Table 5). Therefore, it is obvious that the method is only suitable for process control of one particular company with relatively similar excipients, rather than for market quality control with unknown matrix.

Table 5 Predicted and actual values of NFX in validations against different matrixes

Sample ID	Actual NFX (mg/g)	Predicted NFX (mg/g)	Error (%)
T5	0.3480	0.3919	12.6%
T6	0.4170	0.5174	24.1%
T7	0.3273	0.4189	28.0%
T8	0.3810	0.3906	2.5%
T9	0.4288	0.3661	-14.6%
T10	0.4685	0.3753	-19.9%
T11	0.5394	0.4301	-20.3%
T12	0.4101	0.5956	45.2%
T13	0.3868	0.6954	79.8%
T14	0.3614	0.6015	66.5%

Moisture, having strong NIR absorbance at 1400nm, may cause significant error to the predicted content of

norfloxacin. Therefore, the compound in samples with varied moisture contents (M1-M5) were determined.

Table 6 Predicted and actual values of NFX for samples with varied moisture contents

Sample ID	% moisture	Actual NFX (mg/g)	Predicted NFX (mg/g)	Errors
M1	0.61	0.2958	0.3135	6.0%
M2	1.91	0.3711	0.4656	25.5%
M3	2.28	0.2913	0.3770	29.4%
M4	3.15	0.3391	0.4687	38.2%
M5	5.62	0.3816	0.5492	43.9%

From the obtained results, we observed that moisture have strong effect on the quantitative results, therefore, drying of samples is necessary to minimize the errors.

Pereira *et al.* (2016) performed the quantitation on FT-NIR for nevirapine and obtained the prediction error of $-5.1 \div 8.7\%$ and $-4.6 \div 3.3\%$ [21]. Meanwhile, an unprecedented mean error of prediction of 0.8% was reported by Alcalá *et al.* (2014), using a portable JDSU MicroNIR[16]. That could be the results of the performance and hence the cost of the instruments as well as sampling techniques. Since our NIRscan Nano (Texas Instrument) is much more affordable, and as a result, the sensitivity and resolution are not as that good. In addition, the sampling and measuring procedure have not been optimized and standardized which certainly have great impact in the quality of the spectra. In future work, our objectives are to improve both RMSEE, RMSEP, so that the errors meet the requirement of pharmaceutical industry. That could be done by either trying standardizing the sampling technique with

our instrument or use other instruments with higher resolution.

4 Conclusions and future work

This paper has presented the potential of combining spectroscopy with chemometrics for qualitative and quantitative analysis and promising results for low-cost handheld NIR in the case of pharmaceuticals. Adulterants (sesame, sunflower, soybean) were differentiated from authentic olive oil and could be quantified with error $< 5\%$. Norfloxacin content in powder were rapidly determined by handheld NIR in the range of 90- 500mg/g with studied effects of excipients matrix and moisture.

In the future, our efforts are to focus on the improvement of the quantitation accuracy and to develop procedures for more delicate and detailed classification. To achieve those, it is highly desirable to build a larger data set for better pattern-recognition with optimized spectra acquisition process, more importantly, to validate our models with external samples and reference methods. Our collaboration with industries, applied mathematics and informatic technology groups opens the possibility to develop an algorithm that can replace manual work and available for online data processing.

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Hướng tiếp cận bằng phương pháp thống kê đa biến trong quản lý chất lượng thực phẩm và dược phẩm

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Tóm tắt Phổ IR chứa nhiều thông tin về cấu trúc hóa học của mẫu vật ở dạng thô không xử lý. Tuy nhiên phổ IR thường phức tạp nên không sử dụng trực tiếp để định tính và định lượng. Trong nghiên cứu này, đã sử dụng phương pháp phân tích dữ liệu đa biến (hay còn gọi là chemometrics) để xác định thành phần hoá học từ dữ liệu phổ thu được. Bài báo trình bày 2 thí dụ để minh chứng cho tiềm năng ứng dụng của phương pháp này trong hoá phân tích. Hai ứng dụng đó là phân tích dầu ăn bằng máy FT-IR dạng để bàn, và phân tích dược phẩm bằng máy NIR cầm tay. Với công cụ PCA dầu olive có thể dễ dàng phân biệt với các loại dầu thực vật khác như dầu mè, dầu cò, dầu hướng dương, đậu nành. Thành phần dầu olive trong hỗn hợp với các loại dầu khác cũng có thể định lượng bằng PLS với sai số <5%. Với đối tượng dược phẩm, hàm lượng norfloxacin trong viên thuốc dạng rắn có thể được xác định với sai số <6%. Kết quả cho thấy phương pháp trên rất có tiềm năng trong việc phân tích nhanh với chi phí rất thấp.

Từ khóa chất lượng thực phẩm và dược phẩm, chemometrics, máy NIR cầm tay, phân tích dữ liệu đa biến